THE DEVELOPMENT OF METHODS FOR DETERMINING BASAL METABOLISM OF MANKIND

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When we breathe, oxygen is absorbed from the air in the lungs and carried by the blood to all parts of the body. The oxygen unites with the protein, fat, and carbohydrate available, produces carbon dioxide and water and in this oxidation process heat is generated. Lavoisier (1), in 1777, discovered that animals confined in an enclosed space absorbed oxygen from the enclosed air and gave off carbon dioxide. Later he and La Place (2) found that the heat given off by a guinea-pig in an ice calorimeter nearly equalled that which would be produced in the same length of time by the oxidation of the carbon equivalent to that given off in the carbon dioxide produced by the guinea-pig. They thus established a relationship between direct and indirect calorimetry. In 1789 Seguin and Lavoisier (3) made their respiration experiments on man without food at two environmental temperatures, thus determining the first basal metabolism values on a human subject. We do not have all the details of the apparatus used, but we know that a face mask was employed and that the expired air was collected and then analyzed for oxygen and carbon dioxide. Since that time various methods have been used to measure the products of combustion in the body, the carbon dioxide excreted or the oxygen absorbed, or directly the heat eliminated. I shall mention some of the methods with respect to various types that have been developed and modified from the time of Lavoisier to the present day. It is impracticable to describe in detail all of the apparatus used, but I hope to show in a general way the gradual development of the methods and apparatus up to the present-day simplifications and refinement.

Allen and Pepys (4), in 1808, described an apparatus in which the subject breathed through a mouthpiece. By means of valves operated by hand, the subject inspired from a gasometer with water as a seal and expired into gasometers with mercury as a seal. Only the carbon-dioxide production was measured.

Andral and Gavarret (5), in 1843, used a copper mask with rubber edges, which could be fitted to the face. This had valves which prevented the subject from expiring into the outside air. A tube was connected to a series of glass globes in which a vacuum had been established before the experiment began. The expired air was collected by suction, and subsequently the carbon dioxide in this air was absorbed and the increase in weight of the absorption train determined.

Smith (6), in 1859, used a metal mask with valves, a meter to measure the inspired air, and containers with sulphuric acid and potash solution to absorb water vapor and carbon dioxide. Figure 2 shows the arrangement of the apparatus. The box container for the potash solution and the sulphuric acid container following it were weighed to obtain the output of carbon dioxide.

C. Speck (7), in 1871, used a pair of gasometers, one for the inspired air and one for the expired air. A nose clip closed the nostrils, and breathing took place through a tube placed in the mouth. Valves were employed to separate inspired and expired air. The changes in the weights of the bells of the gasometers were compensated by decrease and increase in weights in the counterpoises. A sample of expired air was analyzed for both carbon dioxide and oxygen.

Regnard (8), in 1879, collected the expired air in a rubber bag of about 200-liter capacity. The breathing was through a mouthpiece, and the inspired air was separated from the expired air by valves. A sample of the air in the bag was later analyzed. The modern counterpart of the bag method is the wedge-shaped bag devised by Douglas (9) in 1911. This is transportable and may also be used in rest experiments. The chief criticism against the use of rubber for collection of expired air is its permeability to carbon dioxide. This has been recently overcome by Mueller (10), who coated the inside of the bag with tinfoil and then vulcanized it.

In 1887 Geppert (11) reported measurements of the total expired air by a wet meter and had an arrangement for drawing duplicate proportional samples directly into a gas analysis apparatus. The samples were subsequently analyzed for carbon dioxide and oxygen.

Hanriot and Richet (12) in 1891 adopted a principle in the determination of the respiratory exchange that is very simple theoretically. They employed three meters in series. The first meter measured the volume of inspired air, the second meter measured the volume of expired air, and the third the volume of expired air after the carbon dioxide had been absorbed. The difference between the first and third meters gave the volume of oxygen absorbed. A mask and Mueller (water) valves were used for separating inspired and expired air.

Scharling (13), in 1843, had a chamber of 1 cubic meter content suitable for humans. It was ventilated by an air pump or aspirator, and the entire air was conducted through a potash solution to absorb the carbon dioxide. The ingoing air was also freed from carbon dioxide by a potash solution.

Pettenkofer (14), in 1862, constructed a chamber large enough for a man to remain in it 24 hours or more. The chamber was continually ventilated, and the ingoing and the outgoing air were continuously sampled proportionately for carbon dioxide and water vapor. The water vapor was absorbed by sulphuric acid and the carbon dioxide by barium hydroxide, which was afterward titrated. The total ventilation through the apparatus and sampling arrangements was measured by gas meters.

Liebermeister (15), in 1870, constructed a chamber suitable for a man, and of such a shape that the subject could sit or recline. The chamber was ventilated, and the carbon-dioxide production was determined periodically in small samples of the outgoing air by absorbing the carbon dioxide in a barium hydroxide solution and later titrating the solution with oxalic acid. He then constructed a graph of the changes in composition of the outgoing air and by means of a differential equation expressing the relationship between the ventilation, the time elapsed between samples, and the carbon-dioxide content of the outgoing air, he was able to calculate the carbon-dioxide production.

The principle of determining the respiratory exchange with a chamber by conducting air through the chamber and passing samples of the ingoing and outcoming air through absorbers as applied by Pettenkofer and Voit, has been employed by a number of other workers. The early form of the respiratory calorimeter in Middletown, Connecticut, described by Atwater, Woods, and Benedict (16) in 1897 utilized this principle. A special pump was devised for withdrawing an aliquot of the air leaving the chamber, and this aliquot was subsequently passed through absorbers for water vapor and carbon dioxide. This chamber was large enough for a man to live in for days and weeks at a time.

In 1903 Jaquet (17) described an irregular shaped chamber of such a size that a man could either sit in the apparatus or could recline upon a bed. The outcoming air was measured by means of a gas meter, and an aliquot sample was taken for analysis. This was subsequently analyzed for carbon dioxide and oxygen.

In 1910 (18) Grafe published a description of his respiration chamber for bedridden patients only, the top of which could be raised easily in order to roll in a patient on the bed. In 1909 (19) he also described his head respiration apparatus, an arrangement that covered the head and shoulders of the patient. Both of these apparatus of Grafe were ventilated on the open-circuit principle, and an aliquot sample of the outcoming air was analyzed for carbon dioxide and oxygen.

A chamber of large size that would hold more than one person was constructed by Sondèn and Tigerstedt (20) and described in 1895. Only the carbon-dioxide production was determined with this chamber apparatus. In 1919 Benedict (21) reported the construction of a large group chamber capable of holding at least twelve individuals in bed, by which the carbon dioxide elimination of a group could be determined. The aliquoting of the outgoing air was by a unique principle.

Not only did Lavoisier study the respiratory exchange by the open-circuit principle but also he made some experiments on the respiratory exchange of animals in a closed system. This principle, however, was not carried out with man until a number of years later.

The principle of the closed-circuit system of Regnault and Reiset (22) was applied to man by Hoppe-Seyler (23) in 1894. The carbon dioxide was absorbed from the air by means of a potash solution, and oxygen was admitted to the system through a gas meter. The carbon dioxide was afterwards driven off from the potash solution by means of sulphuric acid and absorbed in an apparatus for carbon dioxide, and the apparatus was weighed. The oxygen used was obtained from the readings of the gas meter and from an analysis of the air in the respiration chamber.

In 1905 (24) the respiration calorimeter at Middletown, Connecticut, was brought to a state where the respiratory exchange of man in a chamber could be determined in short periods of from one to six hours with a high degree of accuracy. Subsequently the general principle and mechanical arrangements used in this apparatus were applied to the construction of respiration calorimeters in the Nutrition Laboratory (25). With the closed-circuit system of both the Middletown and Boston calorimeters the water vapor elimination and the carbon-dioxide excretion were determined by absorption in weighable containers, correcting for the changes in composition of the air in the closed system from the beginning to the end of the period. Oxygen was admitted from a weighed cylinder and the oxygen absorption determined from the changes in composition of the air in the system and the oxygen admitted from the weighed cylinder. In 1913 (26) observations were begun at Bellevue Hospital, New York, with a closed-circuit respiration calorimeter for bedridden patients constructed by the Russell Sage Institute of Pathology on the same general principle as the respiration calorimeters in Boston.

In 1909 appeared the first description (27) from the Nutrition Laboratory of a respiration apparatus for the determination of the respiratory exchange and respiratory quotient of man in short periods. This apparatus was the outcome of the application of the principle used in the large respiration calorimeters in Wesleyan University at Middletown and in the Nutrition Laboratory at Boston. The general principle was the determination of the carbon-dioxide elimination by absorbing it in soda-lime in weighable containers. Oxygen was admitted to the apparatus from a weighed cylinder to compensate for the amount absorbed by the subject, and the indicator for the admission of oxygen was the rise and fall of a bathing cap connected with the circulating air. The attachment to the subject was made by means of pneumatic nosepieces. This respiration apparatus was subsequently improved (28) and the bathing cap was replaced by a spirometer, the movements of which were recorded on a kymograph, thus giving an index of the character of the respiration. The volume of oxygen admitted was determined not by weighing the cylinder containing the supply, but by passing the oxygen through a carefully calibrated meter. This apparatus was called the "universal respiration apparatus" because the same arrangement could be used for short periods with man, or could be attached to a chamber for obtaining the respiratory exchange of an animal.

In 1916 Benedict and Tompkins (29) described a clinical respiration chamber principally designed for the accurate determination of the respiratory quotient in periods of one hour or longer. This utilized a form of the universal respiration apparatus, but the chamber was of the smallest capacity that could be used and still have a subject comfortable inside it.

In 1918 Benedict (30) reduced the universal apparatus to a much smaller form. Calcium chloride was used instead of sulphuric acid for absorption of water vapor, and the apparatus was so compact that it was transportable, that is to say, it could be moved from one room to another in a hospital without dismantling and without extra assistance. This still permitted the determination of the respiratory quotient as well as the oxygen absorption.

In 1920 (31) the portable or transportable apparatus was somewhat more simplified by eliminating the determination of the carbon-dioxide excretion and making the apparatus suitable for the determination of oxygen only. This apparatus was strictly portable, as it could be shortened or altered in such a way that transportation could be made by hand.

A simple and inexpensive apparatus for use by students was described by F. G. and C. G. Benedict (32) in 1923. The inauguration of the studies on racial metabolism led to the development of a field form of the student apparatus that could be easily disassembled, transported, and reassembled in the field for use in measurements of the metabolism of different races (33). This has proved of immense practical value and has functioned satisfactorily in studies of the basal metabolism of different racial groups all over the world and under unusual conditions.

The closed-circuit apparatus for the determination of the respiratory exchange of man in short periods has found wide application in European laboratories as well as American institutions. During the last decade a number of modifications have been devised, with especial reference to the determination of both carbon dioxide and oxygen. Among these may be mentioned those of Hagedorn (34), of Knipping (35), and of Helmreich and Wagner (36) in 1924, and those of Dethloff (37), and of Dusser de Barenne and Burger (38) in 1925. However, we have come to the conclusion that the best method of determining the respiratory quotient, when this is necessary, is by the use of the helmet of Benedict (39) with an open-circuit apparatus, two blowers, and a spirometer or bathing cap, and meters. An aliquot sample is analyzed by the gas-analysis apparatus devised in the Nutrition Laboratory (40). With this apparatus it is possible to determine the carbon-dioxide and oxygen content of air to 0.003 per cent. Hence the apparatus can be ventilated at a rate rapid enough so that the carbon-dioxide content of the outcoming air will be under one per cent. This system gives the optimum opportunity for normal breathing and repiratory quotients with a high degree of accuracy.

Each one of us is losing weight at the present moment. On the average this loss amounts to about one-half gram per minute. This loss in weight, which is called the "insensible perspiration," is due to the fact that the sum of the vaporization of water and the elimination of carbon dioxide is greater than the absorption of oxygen. F. G. Benedict (41) has been investigating this loss in weight for a number of years. By means of a delicate balance he was able to measure the loss of a subject in periods as short as 10 minutes. In a cooperative research with Dr. H. F. Root (42) at the New England Deaconess Hospital in Boston, a relationship has been established between the hourly insensible loss and the metabolism. This method of estimating the basal metabolism promises to be useful with patients who can not or will not tolerate a direct measurement of the respiratory exchange.

Thus far we have dealt only with apparatus for determination of the respiratory exchange. At the beginning of this lecture I pointed out the connection between respiratory exchange and heat production first conceived by Lavoisier. Relatively few apparatus have been constructed for the direct determination of heat elimination and heat production in man. In 1892 Atwater and Rosa (43) began the construction of a respiration calorimeter at Wesleyan University, Middletown, Connecticut. Subsequently this was brought to a high state of perfection by Atwater and Benedict (44). In 1907 and 1908 calorimeters on the same principle were built in Boston at the Nutrition Laboratory (45). One was a bed calorimeter for subjects in the reclining position, and with this many of the earlier observations on the basal metabolism of humans were obtained. Subsequently, as mentioned before, a respiration calorimeter was constructed by Du Bois and his associates at the Russell Sage Institute of Pathology in New York, and this has been much used in studies in disease.

In 1924 Noyons (46) described a calorimeter constructed on the differential or comparison principle. For a number of years at the Nutrition Laboratory there has been in use a calorimeter for humans on the differential or comparison principle. Although the observations with calorimeters have not been so numerous as those with the respiration apparatus, they have been of fundamental importance in establishing the general principle that the heat production obtained by the indirect method, that is, from the respiratory exchange, is comparable with that obtained directly by the calorimeters.

Choice of apparatus. In the determination of the basal metabolism, one of the first problems encountered is the choice of apparatus. Should one buy a simple portable type of apparatus for the measurement of oxygen absorption only, or should one secure more complicated apparatus necessitating a gas-analysis apparatus and gasometers for the open-circuit method and for the determination of the respiratory quotient? Only a few institutions determine the basal metabolism by the direct measurement of heat production, because of the large amount of funds and the large personnel required for such observations. Before considering the question of the apparatus to secure, we should have in mind what we are trying to measure. In the body three classes of substances are burned, protein, fat, and carbohydrate. Each of these has a specific amount of heat production per unit of material, and in the process of generating heat, carbon dioxide is produced as the result of oxidation and oxygen is absorbed in order to carry on the process. Table I shows the volume of carbon dioxide given off and oxygen absorbed and the heat produced in the body in the combustion of 1 gram of each of these three substances. Now we may measure directly the heat elimination and with suitable correction for the change in body temperature we may obtain the heat production, but as already pointed out, this is an expensive and complicated procedure. At the present time, therefore, the heat production is usually determined indirectly, that is, by measurement of the respiratory exchange. Along with measurements of the carbon-dioxide production and the oxygen consumption, some investigators also determine the nitrogen eliminated in the urine, since the latter comes specifically from the metabolism of protein. From these measurements the heat production is calculated as follows: The grams of nitrogen in the urine are multiplied by the factor 6.25 to obtain the grams of protein burned. The value for grams of protein burned is then multiplied by the theoretical volume of carbon dioxide produced and by the theoretical volume of oxygen absorbed in the combustion of one gram of protein. The volumes of carbon dioxide and oxygen thus obtained are substracted from the measured total volume of oxygen consumed and the measured total volume of carbon dioxide produced. The results represent the sums, respectively,

TABLE I.

GASEOUS EXCHANGE AND HEAT PRODUCTION OF CARBOHYDRATE, FAT, AND PROTEIN.

(Amounts per gram.)

NUTRIENT	CO_2 cc.	O_2 cc.	R. Q.	CALORIES
Human fat	1,420	1,990	0.713	9.54
Glycogen	829	829	1.000	4.20
Protein	774	957	0.809	4.40

of the carbon dioxide production and the oxygen absorption due to the combustion of carbohydrate and fat. By means of simultaneous equations we may then calculate the weights of fat and carbohydrate burned. Finally, from the known caloric values of protein, fat, and carbohydrate we can determine the heat due to the combustion of each of the three substances. The sum of these heat values gives the total amount of heat produced as obtained by the indirect method.

This method necessitates time-consuming and tedious calculations in addition to the measurement of the respiratory exchange and the determination of the nitrogen in urine. If all basal metabolism measurements required this complicated procedure the number of metabolism measurements that could be made would be reduced considerably. An alternative method is to measure both the oxygen consumption and the carbon-dioxide production but to disregard the protein metabolism because it usually constitutes only 15 per cent of the total metabolism and because in the combustion of protein the caloric value of oxygen per liter is nearly like that in the combustion of fat and of carbohydrate and the respiratory quotient is between that of fat and that of carbohydrate. A third and still simpler method is to disregard the determination of the respiratory quotient and measure only the oxygen absorption. The question arises as to what justification there is for either neglecting the protein or for assuming that one can obtain reliable and accurate results from the measurement of oxygen absorption alone. A number of writers on the subject of metabolism have pointed out that there is a wide variation in the possible ranges of respiratory quotients and have implied that there is the same wide range, percentagewise, in the heat production under the different respiratory quotients. However, one can see from the values in the table that between the quotients of 0.70 and 1.00 the range in caloric value of oxygen is not over 7 per cent. Hence it is the usual practice to calculate the heat production from the measured oxygen consumption, using the caloric value of oxygen at an assumed respiratory quotient of 0.82, namely, 4.825 calories per liter.

The question is, how close do we obtain the true heat production from the determination of the oxygen consumption alone? To answer this question, we have calculated, from an example from our own work, the heat production according to the three different methods of measurement just described.

Example of Three Different Methods of Calculating Total Heat Production.

(Values per minute.)

156 c. c. CO_2 | Nitrogen in urine
185 c. c. O_2 | 0.00625 gram
0.84 R. Q.

Heat production calculated from

Protein, fat, and carbohydrate	= 0.905 cal.
Measured O_2 and measured R. Q.	= .898 cal.
Measured O_2 and assumed R. Q. of 0.82	= .893 cal.

In the example we had at our disposal for calculation the following factors: 156 c.c. of carbon dioxide per minute, 185 c.c. of oxygen per minute, with a consequent respiratory quotient of 0.84 and a nitrogen elimination of 0.00625 gram per minute. If the protein metabolism is taken into account, the heat production calculated from these figures is 0.905 calorie per minute. If we accept the idea that the respiratory quotient is necessary for the exact calculation of the heat production and use the caloric value of oxygen at the respiratory quotient obtained in this case, we shall have 0.898 calorie. In this result we have employed the same values for carbon dioxide and for oxygen as we did in the first condition. In the third method of calculation we have used the oxygen measurement alone and have assumed a respiratory quotient of 0.82. Multiplying the oxygen figure by its caloric value for this respiratory quotient we obtain 0.893 calorie. Therefore, the three different methods of deriving the heat production give results ranging from 0.893 to 0.905 calorie per minute. One is justified in using methods that involve only the determination of oxygen for obtaining the basal heat production.

Having come to the conclusion that we are to measure the basal heat production by the indirect method and by the determination of the oxygen consumption alone, we still have further the question of selection of apparatus. For the average clinic the Roth modification (47) of the Benedict apparatus would appear to be the simplest form. This, however, requires effort on the part of the subject to open valves and to raise and lower a spirometer. For the most normal breathing conditions, we believe that an apparatus with a motor device is more suitable. Indeed, the best for this purpose is the apparatus modified in recent years by Benedict (48), in which a soda-lime container and a rotary blower are used and a spirometer serves as a dead end to the system. If a helmet is used as a breathing appliance instead of the mouthpiece, there is the greatest freedom from annoying conditions such as flow of saliva, uncomfortableness of the mouthpiece and particularly the noseclip. In recent series of observations, the helmet has been shown to be reliable and extremely comfortable, in fact, practically all individuals who have tried it prefer it to the mouthpiece. All apparatus of the spirometer type should have in connection with them a kymograph record of the excursions of the spirometer bell. If funds are limited, or if the work is in the field, and great portability is desired, the Benedict field respiration apparatus (33) is undoubtedly extremely useful. Indeed, this apparatus has proved itself of value already in a number of investigations in the field, notably in the West Indies and in Yucatan.

Normal test of apparatus. Every laboratory working on the determination of basal metabolism should test the accuracy of its apparatus with a normal subject. When the fact is once established that the apparatus will give results on this normal subject within what is considered the normal range, this same subject's metabolism should be measured periodically in order to control the continued correct functioning of the apparatus. It is not sufficient to test the apparatus solely at the beginning of a series of measurements or when it is first installed. This subject should be called upon to act as a control whenever there is doubt as to the measurements which have been made upon a patient, and when such a person is used as a control the test should be made under as nearly as possible the same conditions as those which prevailed when apparently abnormal results were obtained with a patient. As Du Bois has pointed out, no work is better than its controls.

Theoretical test of apparatus. The best theoretical test of any type of respiration apparatus is the burning of a definite quantity of ethyl alcohol. The most all-round useful apparatus for this purpose is the combination of kymograph (49) or windshield wiper (50) and burette and spirometer, in which the small spirometer acts as a breathing apparatus and the burette is raised gradually so that the amount of alcohol burned can be measured.

Testing of apparatus during experiment. Much of the earlier work has been vitiated by the lack of an adequate test for the tightness of the apparatus during the actual measurement. With the closed-circuit and spirometer unit this test can be easily made by placing 30 grams (51) on the spirometer bell and observing whether there is any change in the level of the bell, either as indicated by the kymograph curve or by readings on the millimeter scale of the spirometer. If the slope of the kymograph curve or the curve of the plotted readings during that portion of the period when the weight is on the bell is different from the slope of the curve when the weight is not on the bell, this is proof of the presence of a continuous leak. The occurrence of an occasional leak (such as might be caused by the opening of the mouth or, in the case of the helmet, by movement of the head so that a slight opening is temporarily made in the closure around the neck) will be shown only on the kymograph record and will be indicated by a change in the trend of the curve.

Calculation of results. For the calculation of results a large number of charts, tables, nomograms, and other aids are now available. These are useful for saving time, but anyone who is using a metabolism apparatus should be familiar with and capable of carrying out the calculations without the assistance of the charts and nomograms, even to the extent of doing all the calculations by arithmetic. This is particularly true with regard to technicians who have little knowledge frequently as to the significance of the figures that they are using, and who would in many cases never recognize ludicrous errors in either observations or calculations. It ought to be a regular routine in a laboratory for the operator periodically to carry out calculations by the long process, in order to have a thorough understanding of the methods of calculation and to acquire the ability to recognize abnormal figures when they are recorded.

CONCLUSION.

We have thus traced, in outline at least, the development of the modern respiration apparatus for the determination of basal metabolism of man. We have seen that with extremely simple and relatively inexpensive apparatus, the fundamental observations of the basal metabolism of man can be made in a relatively short period of time. However, we must not be misled by the idea that because the procedure is simple, a lack of rigid, careful attention to details of technique can be tolerated. We should regard the determination of basal metabolism with just as much seriousness of purpose as we would the more complicated and more laborious researches on the balance of income and outgo of matter and energy, from which today's simplification of technique is a logical descendant.

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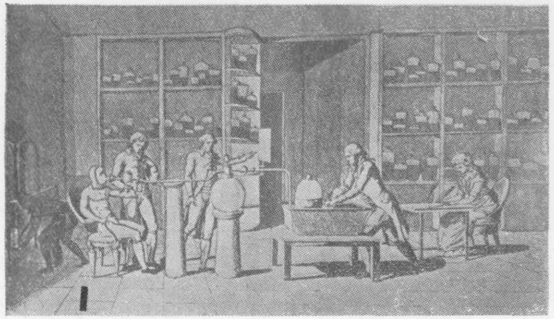

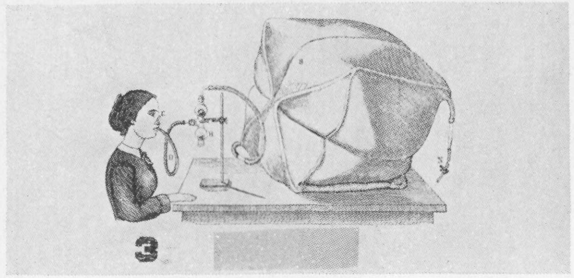

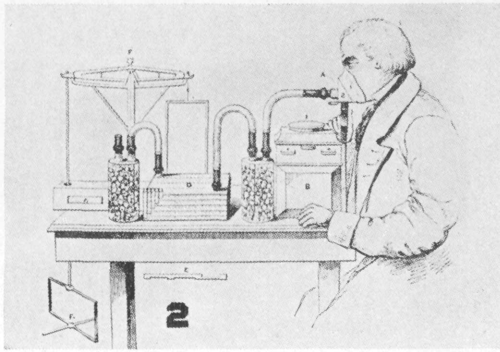

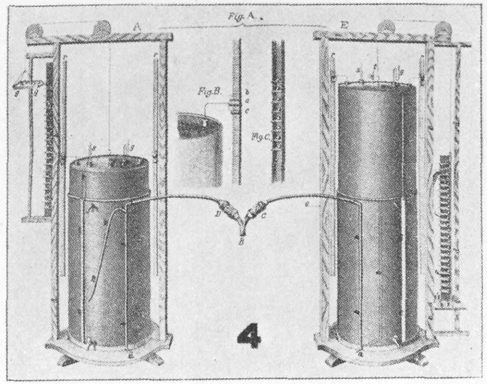

RESPIRATION APPARATUS

Fig. 1. Apparatus of Lavoisier and Seguin (1789).
Fig. 2. Apparatus of E. Smith (1859).
Fig. 3. Apparatus of P. Regnard (1879).
Fig. 4. Apparatus of C. Speck (1892).

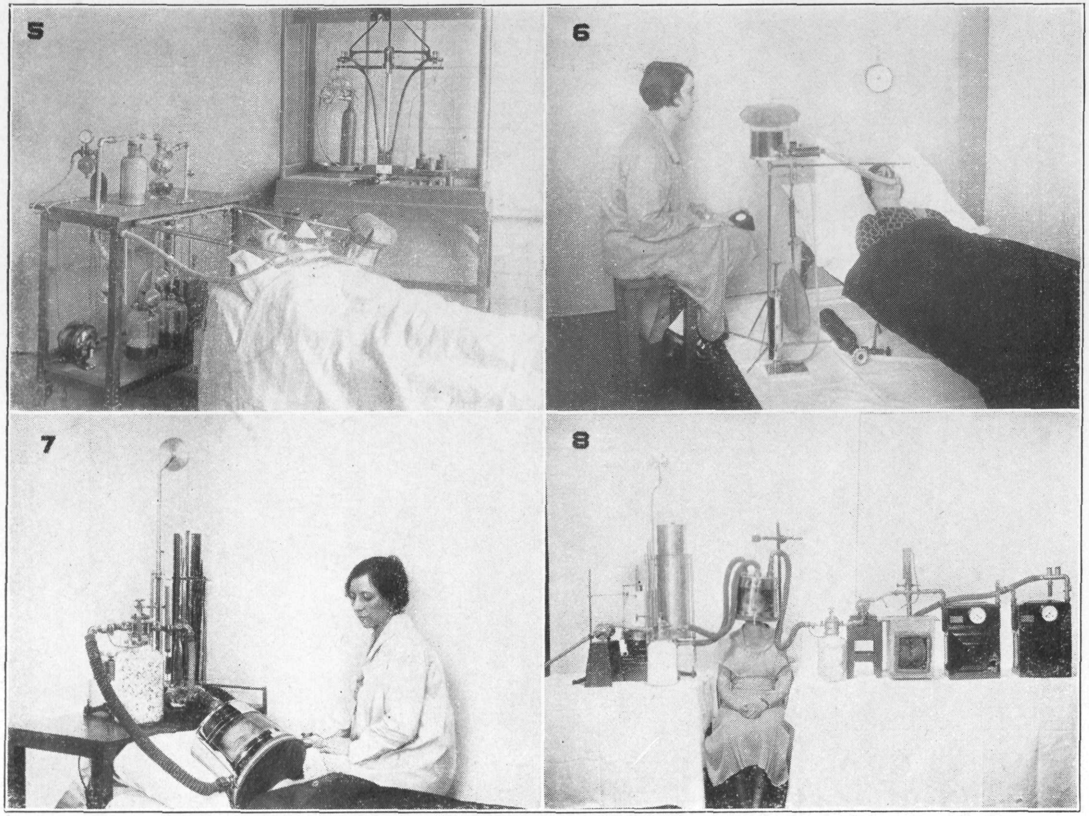

Fig. 5. Closed-circuit respiration apparatus (Benedict, 1909).
Fig. 7. Helmet with closed-circuit respiration apparatus (Benedict, 1930).

Fig. 6. Field respiration apparatus (Benedict, 1927).
Fig. 8. Helmet with open-circuit respiration apparatus (Benedict, 1933).